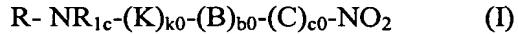


CLAIMS

1. Nitrooxyderivatives or salts thereof having the following general formula (I)



5 wherein

c0 is 0 or 1;

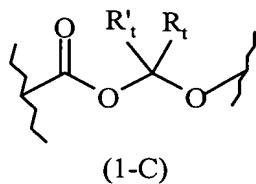
b0 is 0 or 1, with the proviso that c0 and b0 can not be simultaneously 0;

k0 is 0 or 1;

R is the radical of an analgesic drug for chronic pain;

10 R_{1c} being H or straight or branched alkyl with from 1 to 5 carbon atoms;

K is (CO) or the bivalent radical (1C) having the following formula:



wherein the carbonyl group is bound to T₁; R_t and R'_t, same or different, are H, C₁-C₁₀-alkyl, phenyl or benzyl, -COOR_y, in which R_y = H, C₁-C₁₀-alkyl, phenyl, benzyl;

15 B = -T_B-X₂-T_{BI}- wherein

T_B = (CO) or X, in which X = O, S, NH;

with the proviso that:

when b0 = 1 and k0 = 0, then T_B = (CO);

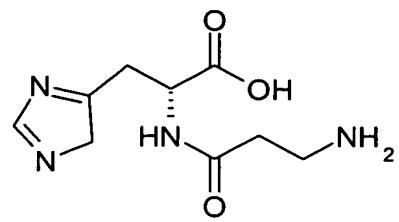
when b0 = 1 and k0 = 1, being K = (CO), then T_B = X as defined above;

20 T_{BI} = (CO) or (X), wherein X is as defined above;

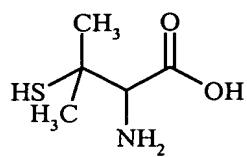
when c0 = 0, then T_{BI} = -O-;

X₂ is such a bivalent bridging group such as the corresponding precursor of B, having the formula Z-T_B-X₂-T_{BI}-Z' in which Z, Z' are independently H or OH, is selected from the following compounds:

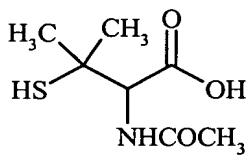
25 - Aminoacids: L-carnosine (CI), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII):



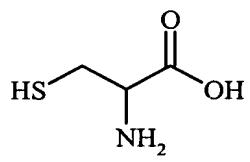
(CI)



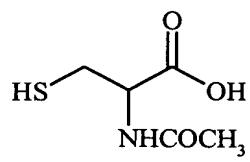
(CV)



(CVI)



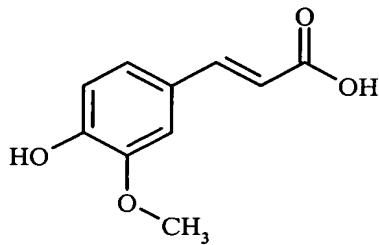
(CVII)



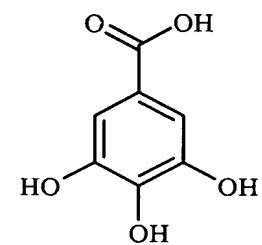
(CVIII)

5

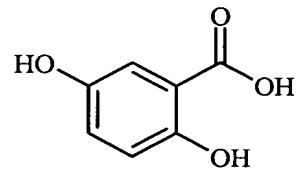
- Hydroxyacids: gallic acid (DI), ferulic acid (DII), gentisic acid (DIII), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), syringic acid (DXI):



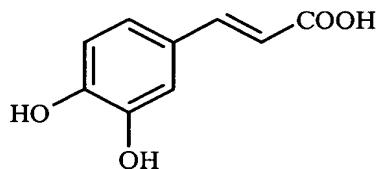
(DII)



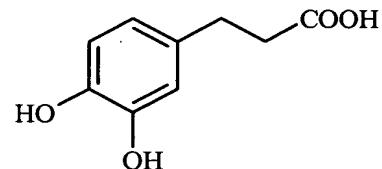
(DI)



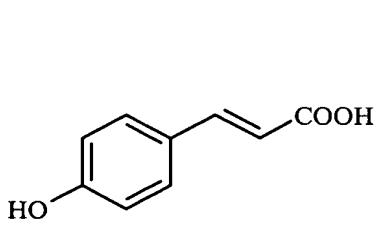
(DIII)



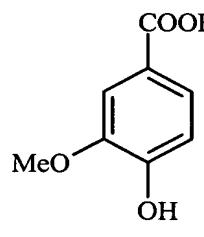
(DV)



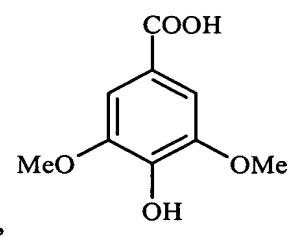
(DVI)



(DVII)

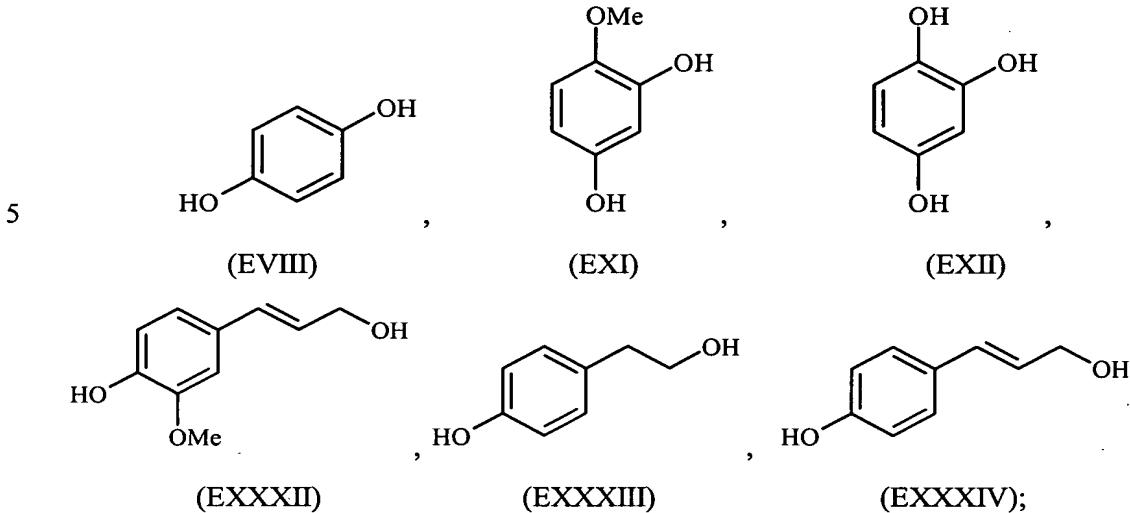


(DVIII)



(DXI)

- aromatic polyalcohols: hydroquinone (EVIII), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), coniferyl alcohol (EXXXII), 4-hydroxyphenethyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV):



10 C = bivalent radical having the formula $-T_c-Y-$

wherein

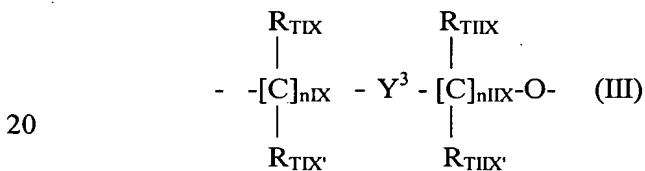
$T_c = (\text{CO})$ or X being as defined above;

with the proviso that when $b_0 = 0$ and $k_0 = 1$:

- $T_c = (CO)$ when $K = (1C)$,

- $T_c = X$ as defined above when $K = (\text{CO})$; and

Y has one of the following meanings:



wherein:

nIX is an integer of from 0 to 5;

nIX is an integer of from 1 to 5;

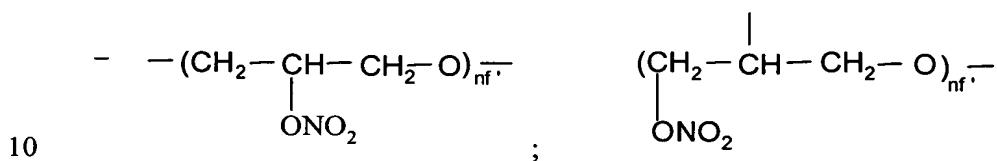
25 R_{TIX} , R_{TIX} , R_{TIIX} , R_{TIX} , the same or different, are H or straight or branched
 C_1 - C_4 -alkyl;

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring with 5 or 6 atoms, containing one to three heteroatoms, said heteroatoms being the same or different and selected from nitrogen, oxygen or sulphur;

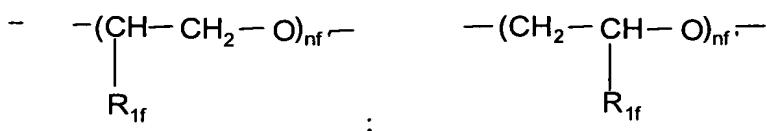
or Y may be:

5 an alkylenoxy group $-R'O-$ in which R' is straight or branched C_1-C_{20} or a cycloalkylene with from 5 to 7 carbon atoms, and wherein in cycloalkylene ring one or more carbon atoms can be replaced by heteroatoms and the ring may present side chains of R' type, R' being as defined above;

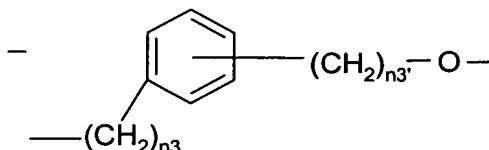
or one of the following groups:



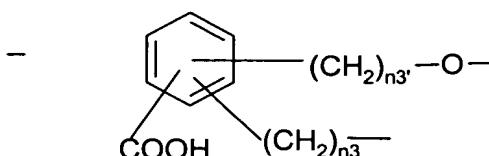
wherein nf' is an integer from 1 to 6;



wherein $R_{1f} = H, CH_3$ and nf' is an integer from 1 to 6;

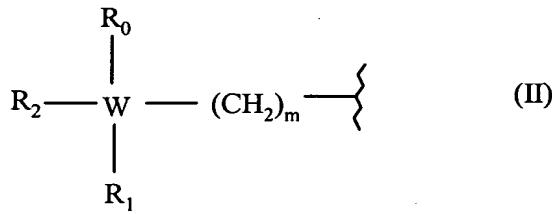


15 wherein $n3$ is an integer from 0 to 5 and $n3'$ is an integer from 1 to 3; or



in which $n3$ and $n3'$ have the meaning mentioned above;

R is the radical of an analgesic drug having formula (II):



wherein:

W is a carbon or nitrogen atom;

m is an integer of from 0 to 2;

5 R₀ = H, -(CH₂)_n-COOR_y, R_y being as defined above;

n is an integer of from 0 to 2;

R₁ = H; when W = N, R₁ is the electronic doublet on nitrogen atom (free valence);

R₂ is selected from the following groups:

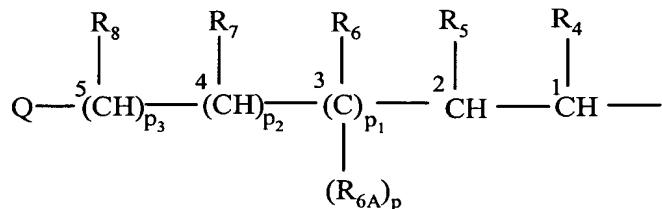
- phenyl, optionally substituted with a halogen atom or with a group selected from

10 -OCH₃, -CF₃, nitro;

- mono or dihydroxy-substituted benzyl, preferably 3,4-dihydroxybenzyl;

- amidino group: H₂N(C=NH)-;

- a radical of formula (IIA), wherein optionally an ethylenic unsaturation may be present between the carbon atoms in position 1 and 2, or 3 and 4 or 4 and 5:



15 (IIA)

wherein:

p, p₁, p₂ are integers, same or different, and are 0 or 1;

p₃ in an integer of from 0 to 10;

R₄ is hydrogen, straight or branched C₁-C₆-alkyl, free valence;

20 R₅ may have the following meanings:

- hydrogen,
- straight or branched C₁-C₆-alkyl,
- C₃-C₆-cycloalkyl,
- OR_A, R_A having the following meanings:

- straight or branched C₁-C₆-alkyl, optionally substituted with one or more halogen atoms, preferably F,

- phenyl optionally substituted with a halogen atom or with one of the following groups: -OCH₃, -CF₃, nitro;

5 R₆, R_{6A}, R₇, R₈, the same or different, are H, methyl or free valence, with the proviso that when an ethylenic unsaturation is present between C₁ and C₂ in radical of formula (IIA), R₄ and R₅ are free valences able to form the double bond between C₁ and C₂; if the unsaturation is between C₃ and C₄, R₆ and R₇ are free valence able to form the double bond between C₃ and C₄; if the unsaturation is between C₄ and C₅, R₇ and R₈ are free valence able to form the double bond between C₄ and C₅;

10 Q is H, OH, OR_B, R_B being benzyl, straight or branched C₁-C₆-alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with a halogen atom or with one of the following groups: -OCH₃, -CF₃, nitro; or

15 Q may have one of the following meanings:

- straight or branched C₁-C₆-alkyl,

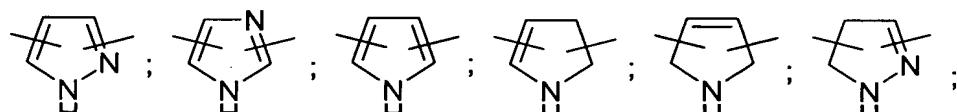
- C₃-C₆-cycloalkyl,

- guanidino (H₂NC(=NH)NH-),

20 - thioguanidino (H₂NC(=S)NH-).

in formula (II) R₂ with R₁ and with W = C form together a C₄-C₁₀ saturated or unsaturated ring.

2. Compounds according to claim 1, characterized in that Y³ in formula (III) is selected
25 from:



(Y1)

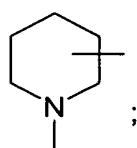
(Y2)

(Y3)

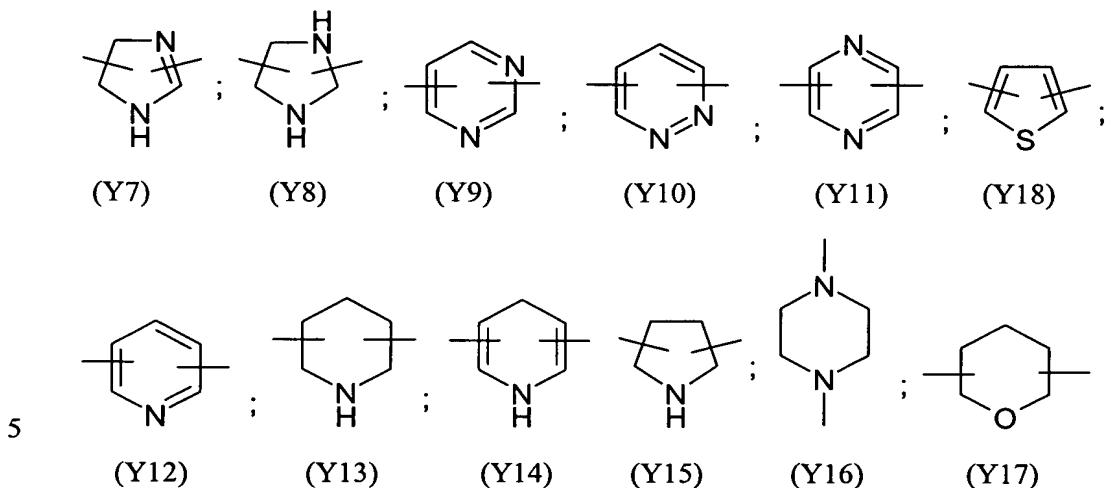
(Y4)

(Y5)

(Y6)



(Y19)



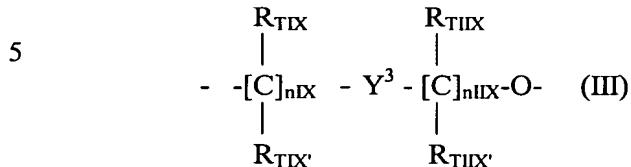
5

3. Compounds according to claim 1, characterized in that in formula (I):

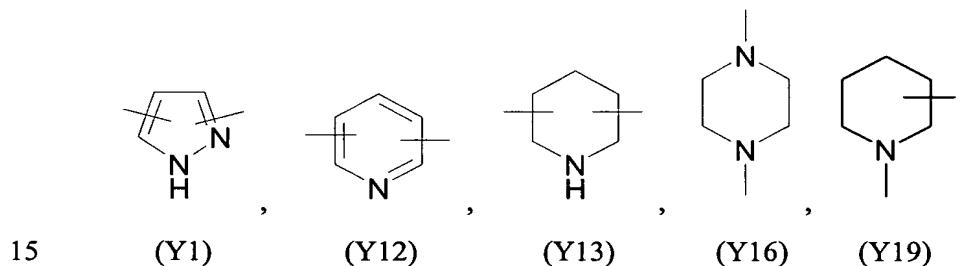
c0 is 1;
10 b0 is 0 or 1;
k0 is 0 or 1;
R_{1c} = H;

K is (CO) or the bivalent radical (1C) as defined in claim 1;
B = -T_B-X₂-T_{BI}- wherein
15 T_B = (CO) or X, in which X = O, S, NH;
with the proviso that:
when b0 = 1 and k0 = 0, then T_B = (CO);
when b0 = 1 and k0 = 1, being K = (CO), then T_B = X as defined above;
T_{BI} = (CO) or (X), wherein X is as defined above;
20 when c0 = 0, then T_{BI} = -O-;
the precursor of B is N-acetylcysteine or ferulic acid;
C = bivalent radical having the formula -T_c-Y-
wherein
T_c = (CO) or X being as defined above;
25 with the proviso that when b0 = 0 and k0 = 1:
- T_c = (CO) when K = (1C),

- $T_c = X$ as defined above when $K = (\text{CO})$; and
 Y has one of the following meanings:

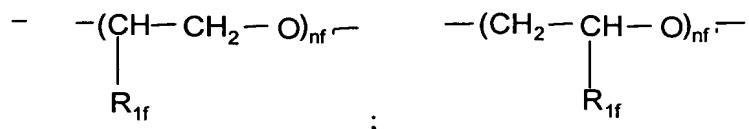


10 wherein:
 $n\text{IX}$ and $n\text{IIX}$ are 1;
 $\text{R}_{\text{TIX}}, \text{R}_{\text{TIX}'}, \text{R}_{\text{TIIIX}}, \text{R}_{\text{TIIIX}'}$ are H;
 Y^3 is selected from the following bivalent radicals:

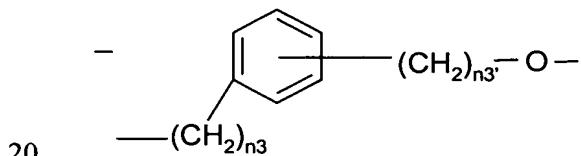


or Y may be:

an alkylenoxy group $-\text{R}'\text{O}-$ in which R' is straight or branched $C_2\text{-}C_6$ alkyl; or

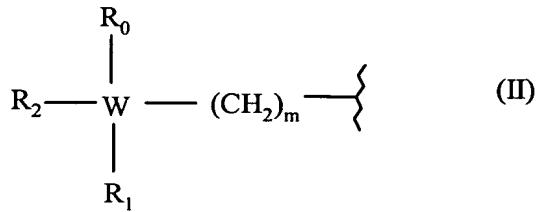


wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 4;



wherein $n3$ is an integer from 0 to 3 and $n3'$ is an integer from 1 to 3;

R is the radical of an analgesic drug having formula (II):



wherein:

W is a carbon atom;

m is 0 or 1;

5 R₀ = H or -(CH₂)_n-COOH, wherein n is an integer of from 0 to 2;

R₁ = H;

R₂ is selected from the following groups:

- 3,4-dihydroxybenzyl; or

- a radical of formula (IIA) as defined in claim 1, wherein:

10 p and p₁ are 0 or 1;

p₂ and p₃ are 0;

R₄ and R₅ are hydrogen, straight or branched C₁-C₆-alkyl or free valence;

R₆ and R_{6A} are H;

with the proviso that when an ethylenic unsaturation is present between C₁ and C₂ in
15 radical of formula (IIA), R₄ and R₅ are free valences able to form the double bond
between C₁ and C₂;

Q is H, CH₃ or

- guanidino (H₂NC(=NH)NH-), or

- thioguanidino (H₂NC(=S)NH-);

20 in formula (II) R₂ with R₁ and with W form together a C₆ saturated ring.

4. Compounds according to claims 1-3, wherein when in formula (II) W = C,

m = 1 and R₀ = -(CH₂)_n-COOR_y, wherein n = 1 and R_y = H; R₂ and R₁ with W as
defined above form the cyclohexane ring; the drug precursor of R having the
formula R-NH₂ is known as gabapentin;

when in formula (II) W = C, m = 0 and R₀ if defined as for gabapentin with n =
0; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅

= R₆ = R_{6A} = H, Q = H; the drug precursor of R having the formula R-NH₂ is known as norvaline;

when in formula (II) W = C, m = 0 and R₀ if defined as for gabapentin with n = 0; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅ = R₆ = R_{6A} = H, Q is the guanidino group; the drug precursor of R having the formula R-NH₂ is known as arginine;

when in formula (II) W = C, m = 0 and R₀ if defined as for gabapentin with n = 0; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅ = R₆ = R_{6A} = H, Q is the thioguanidino group; the drug precursor of R having the formula R-NH₂ is known as thiocitrulline;

when in formula (II) W = C, m = 1 and R₀ if defined as for gabapentin with n = 1; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = p₂ = p₃ = 0, R₄ = H, R₅ = Q = CH₃; the drug precursor of R having the formula R-NH₂ is known as pregabalin;

when in formula (II) W = C and has (S) configuration, m = 1 and R₀ if defined as for gabapentin with n = 1; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = p₂ = p₃ = 0, R₄ = H, R₅ = Q = CH₃; the drug precursor of R having the formula R-NH₂ is known as (S)3-isobutylGABA;

when in formula (II) W = C and has (S), m = 0; R₀ = R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅ = R₆ = R_{6A} = H, Q is the guanidino group; the drug precursor of R having the formula R-NH₂ is known as agmatine;

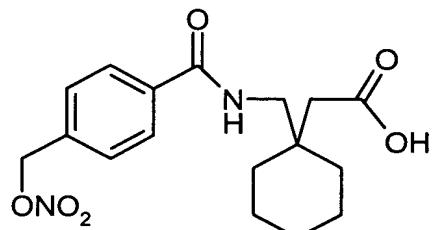
when in formula (II) W = C, m = 0; R₀ if defined as for gabapentin with n = 2; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = p₂ = p₃ = 0, R₄ and R₅ are free valences and between C₁ and C₂ there is an ethylenic unsaturation, Q = H; the drug precursor of R having the formula R-NH₂ is known as vigabatrin;

when in formula (II) W = C, m = 0; R₀ if defined as for gabapentin with n = 0; R₁ = H; R₂ is the 3,4-dihydroxybenzyl radical; the drug precursor of R having the formula R-NH₂ is known as 2-amino-3-(3,4-dihydroxyphenylpropanoic acid (dopa).

5. Compounds according to claims 1-3, wherein the drug precursors of R in formula (I) are selected from lamotrigine, topiramate, zonisamide, carbamazepine, felbamate, amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, tianeptine.

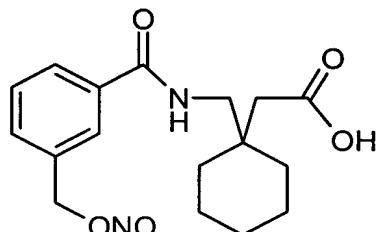
5 6. Compounds according to claims 1, 3 and 4 selected from:

1-[4-(nitrooxymethyl)benzoylaminomethyl]-cyclohexaneacetic acid (XVA),



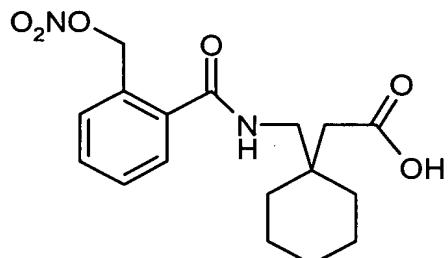
(XVA)

1-[3-(nitrooxymethyl)benzoylaminomethyl]-cyclohexaneacetic acid (XVIA),



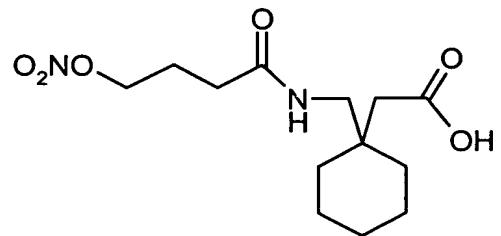
(XVIA)

1-[2-(nitrooxymethyl)benzoylaminomethyl]-cyclohexaneacetic acid (XVIIA),



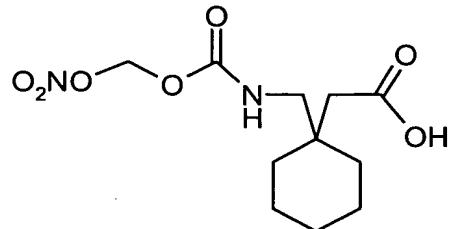
(XVIIA)

15 1-(4-nitrooxybutanoylaminomethyl)-cyclohexaneacetic acid (XVIIIA),



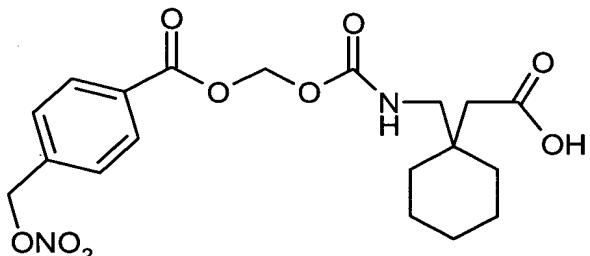
(XVIIIA)

1-(nitrooxymethoxycarbonylaminomethyl)-cyclohexaneacetic acid (XIXA),



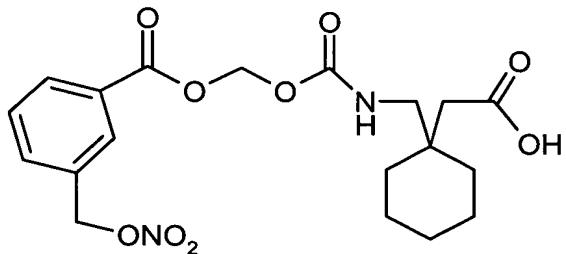
5 (XIXA)

1-{[4-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXA),



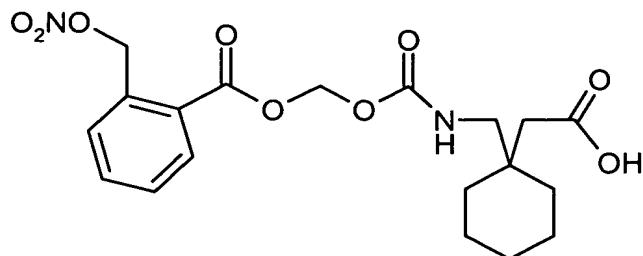
(XXA)

10 1-{[3-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXIA),



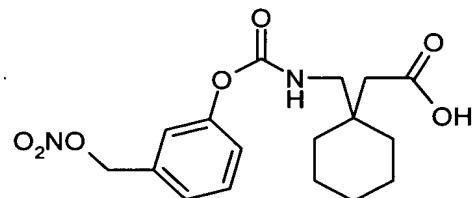
(XXIA)

1-{{[2-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXIIA),



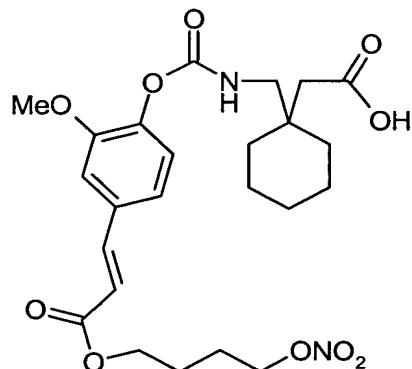
(XXIIA)

5 1-[3-(nitrooxymethyl)phenoxy carbonylaminomethyl]-cyclohexaneacetic acid (XXIIIA),



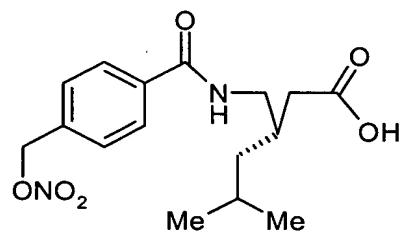
(XXIIIA)

{2-methoxy-4-[(1E)-3-[4-(nitrooxymethyl)phenoxy]-3-oxa-1-propenylphenoxy]-carbonylaminomethyl}-cyclohexaneacetic acid (XXIVA),



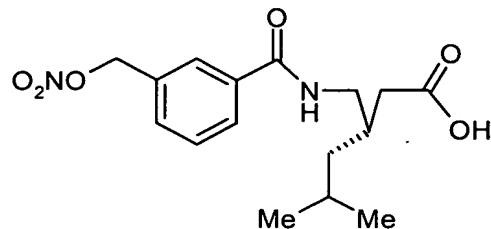
(XXIVA)

3-(S)-[4-(nitrooxymethyl)benzoylaminomethyl]-5-methyl-hexanoic acid (XXVA),



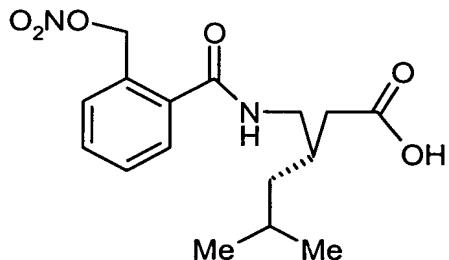
(XXVA)

3-(S)-[3-(nitrooxymethyl)benzoylaminomethyl]-5-methyl-hexanoic acid (XXVIA),



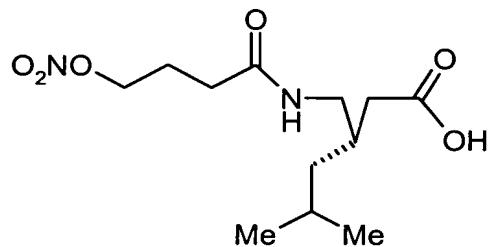
(XXVIA)

5 3(S)-[2-(nitrooxymethyl)benzoylaminomethyl]-5-methyl-hexanoic acid (XXVIIA),



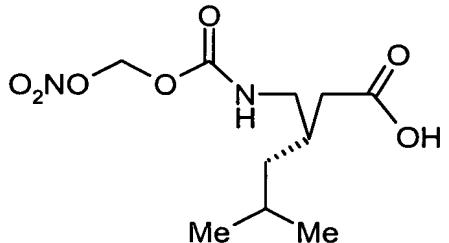
(XXVIIA)

3(S)-[4-(nitrooxybutanoyl)aminomethyl]-5-methyl-hexanoic acid (XXVIIIA),



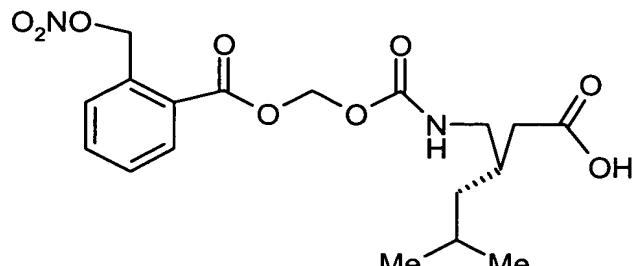
10 (XXVIIIA)

3(S)-[4-(nitrooxymethoxycarbonyl)aminomethyl]-5-methyl-hexanoic acid (XXIXA),



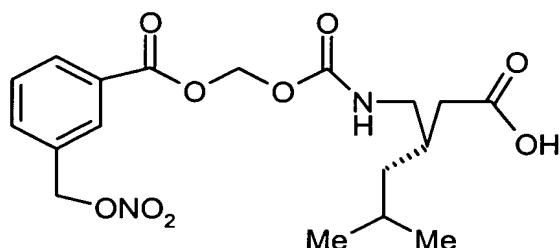
(XXIXA)

15 3(S)-{[2-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-5-methyl-hexanoic acid (XXXA),



(XXXA)

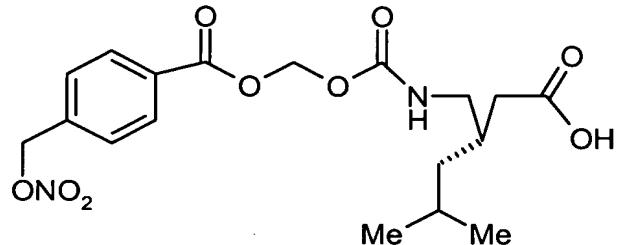
3(S)-{[3-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-5-methylhexanoic acid (XXXIA),



5

(XXXIA)

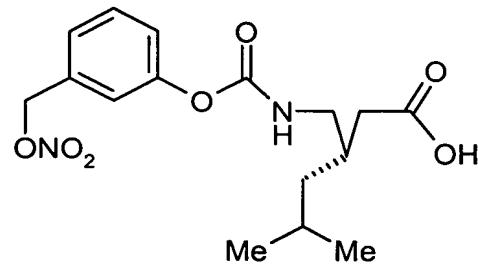
3(S)-[4-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-5-methylhexanoic acid (XXXIIA),



10

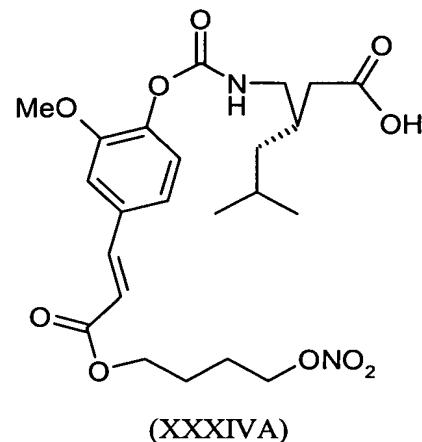
(XXXIIA)

3(S)-[(3-nitrooxymethyl)phenoxy carbonylaminomethyl]-5-methylhexanoic acid (XXXIII A),



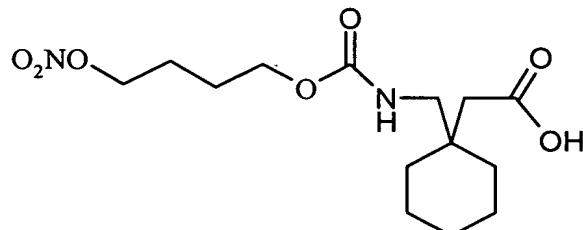
(XXXIII A)

3(S)-{2-methoxy-4-[(1E)-3-[4-(nitrooxybutoxy]-3-oxa-1-propenylphenoxy]carbonylaminomethyl}-5-methyl-hexanoic acid (XXXIVA),



(XXXIVA)

5 1-[4-(nitrooxybutyloxycarbonyl)aminomethyl]-cyclohexaneacetic acid (XXXVA),



(XXXVA)

7. Compounds according to claims 1-6, in combination with NO-donor compounds.

10

8. Compounds according to claim 7, wherein the NO-donors contain in the molecule radicals of the following drugs: aspirin, salicylic acid, ibuprofen, paracetamol, naproxen, diclofenac and flurbiprofen.

15

9. Pharmaceutical compositions comprising compounds according to claims 1-8 as active ingredients.

10. Compounds according to claims 1-8 to be employed as a drug.

20

11. Use of the compounds according to claims 1-8 for preparing drugs for chronic pain.

12. Use of the compounds according to claim 11, wherein the chronic pain is neurophatic pain.